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The Current Status of Thalidomide in the Management of Multiple Myeloma

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Thalidomide · Multiple myeloma

Abstract
Early anticancer research involving thalidomide was abandoned in the 1960s as the catastrophe surrounding the drug emerged, but research efforts were picked up in the 1990s when thalidomide's antiangiogenic and anti-tumour necrosis factor properties were explored. More than 50,000 patients with multiple myeloma are estimated to have been treated with thalidomide to date. Research with thalidomide provides clear and convincing evidence that thalidomide monotherapy is efficacious in relapsed and refractory patients with multiple myeloma. Results typically show a consistent 30% (95% confidence interval 27–32%) response rate (partial response + complete response, defined as a reduction of at least 50% in the monoclonal protein). Thalidomide treatment compares favourably with other typical treatments for multiple myeloma. In seven trials that included 332 patients, vincristine, adriamycin and dexamethasone (VAD) had a response rate of 39% (32–45%), while a trial in 193 patients showed a response rate with bortezomib of 27% (21–34%). The use of thalidomide in combination therapy could boost its efficacy further. More studies to look at the toxicity of the drug need to be carried out. Despite thalidomide's dark past, this drug is of major interest and could be brought back to clinical use in a controlled manner.

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In the past 50 years, thalidomide has made its way from a catastrophic past, which changed the way we look at all drugs, to a profound revival that has surprised many. One of the many astonishing features in the life of this drug is that it never really has been out of use, even though it was not licensed in most countries. A chance finding in 1964 revealed its efficacy in erythema nodosum leprosum (ENL) [1]. Later it was used for Behçet's disease (1979), graft-versus-host disease after allogeneic stem cell transplantation (1988) and a few other conditions. The HIV community in the 1980s discovered that it helps against oral ulceration and wasting. In the United States, pressure was applied to obtain the drug from sources in South America, where it was used for the treatment of ENL. That pressure, and the influence of HIV groups on public opinion, brings thalidomide, the 'dark remedy' [2], back into the forefront of research [3].

As early as the 1960s, some researchers started to look at thalidomide's anti-cancer activity, but this research was quickly abandoned as the catastrophe around the

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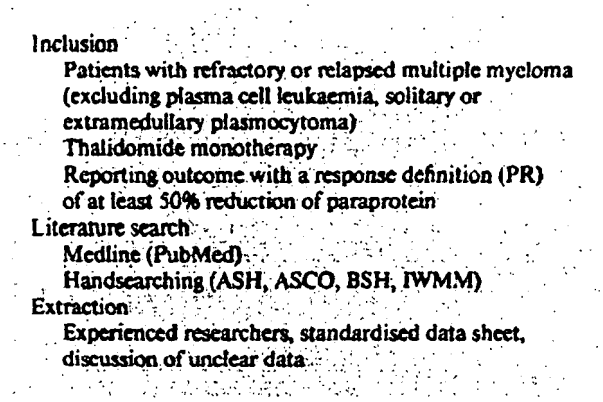

Fig. 1. Methods of systematic review.

Table 1. Trial features and dosing

Features and dosing	Number of trials
Feature	
Data acquisition	
Prospective	16
Retrospective	3
Not reported	10
Study organisation	
Unicentric	18
Multicentric	8
Not reported	3
Consecutive	3
Dosing	
Dosing scheme	
Escalating	26
Fixed	3
Starting dose	
50 mg/day	4
100 mg/day	5
200 mg/day	18
400 mg/day	1
No data	1

drug emerged and the first trials gave negative findings [4, 5]. In the 1990s, the antiangiogenic and anti-tumour necrosis factor properties of thalidomide were explored, but it was the family of a multiple myeloma patient in Little Rock, Arkansas, that started off the development of the drug in this field in 1997. Key data was first presented in 1998 at the American Society of Haematology meeting and then published in 1999 in the *New England Journal of Medicine*, where the authors acknowledged Mrs Beth Wolmer 'for her persistence in recommending the clinical evaluation of thalidomide in the treatment of multiple myeloma' [6]. In 2001, a follow-up report was published [7].

The current status of thalidomide in multiple myeloma can be summarised by two points. First, there is a very clear statement in the British guidelines published by Jamie Cavenagh in 2003 that 'thalidomide is an appropriate therapy for patients with relapsed and refractory disease' and that 'patients not responding to thalidomide alone may respond to the combination of dexamethasone and thalidomide' [8]. Second, as of March 2004, Australia and New Zealand had approved thalidomide as a therapy for multiple myeloma [9]. Thalidomide has not been developed in the classical (top-down) way, according to a strategic plan of its manufacturer, but rather 'bottom-up' – from clinical experience that demonstrated clear and astonishing activity. More than 50,000 patients with multiple myeloma are estimated to have been treated with thalidomide to date; however, thalidomide still lacks a randomised Good Clinical Practice/International Conference on Harmonisation standard clinical trial to document efficacy. It would be impossible, however, to perform such a trial in patients with relapsed or refractory multiple myeloma today, as the efficacy of thalidomide monotherapy is well documented and is now itself considered a standard in this indication. To summarise the available published information on this indication, which is scattered over several studies, our group is currently preparing a systematic analysis of clinical trials that evaluate thalidomide monotherapy in relapsed or refractory multiple myeloma (fig. 1).

As of March 2004 (analysis ongoing), we had identified 49 publications that fulfil the entry criteria. Of these, 20 trials were excluded (16 were duplicate/secondary reports, 4 had no data) and 29 clinical trials with 1,294 patients could be analysed – all were phase II trials without randomisation or comparative groups. Seven of these had been performed in the United States, five in Italy, four in the United Kingdom and three in France. Data acquisition, study organisation and dosing were variable among the trials (table 1).

The target doses were 200, 500 and 600 mg/day in one trial each, 400 mg/day in seven trials and 800 mg/day in 13 trials. Three trials used a fixed-dose schedule. The median dose actually given (reported in 11 trials) was 250, 300 and 500 mg/day in one trial each, 600 mg/day in two trials and 400 mg/day in six trials.

Of the 1,294 patients reported on, 21 were excluded as they had plasma cell leukaemia or were given combi-

Table 2. Response rates

Response	Reduction of monoclonal protein	No. of patients	% (95% CI)
Complete	>90/100%	18	1 (1–2)
Partial	>50%	370	29 (27–32)
Minor	26–50%	173	14 (12–16)
Stable	25→+25%	159	12 (11–14)
Progressive	>+25%	190	15 (13–17)
Not evaluable	Unknown	363	31 (28–33)

nation therapy and 1,273 patients constituted the intent-to-treat (ITT) population of our analysis. No further exclusions were made, and all non-evaluable patients were classified as failures. The median age of the patient population was 63 years, and the median number of previous lines of therapy was one in two trials, two in three trials, three in five trials and four or more in two trials. Table 2 shows the overall response rates in the ITT population (n = 1,273). There was a consistent 30% (95% confidence interval (CI) 27–32%) response rate (partial response + complete response, defined as a reduction of at least 50% in the monoclonal protein).

These results constitute clear and convincing evidence that thalidomide monotherapy is efficacious in relapsed and refractory patients with multiple myeloma. Although an optimal dosing schedule has yet to be established, a schedule that works can be found amongst these trials. Most trials have used an escalating regimen, starting at between 100 and 200 mg per day, to the maximum dose tolerated by the patient. The 12-month survival rates in the trials that reported this outcome were between 50 and 86%.

Thalidomide's efficacy in relapsed and refractory patients is comparable with treatment regimens such as vincristine, doxorubicin and dexamethasone (VAD; seven trials, 332 patients, response rate 39%, 95% CI 32–45%) and bortezomib (one trial, 193 patients, response rate 27%, 95% CI 21–34%).

Although thalidomide's activity as monotherapy was impressively confirmed in this analysis, new published evidence demonstrates an even better efficacy when thalidomide is used in combination with other drugs such as dexamethasone, cyclophosphamide or melphalan. Initial analysis had already shown that dexamethasone in combination with thalidomide given to patients who were progressing on thalidomide alone achieved additional responses [6]. One of the advantages of thalidomide in combination with cytotoxic agents is that it is not, or is only slightly, myelotoxic and allows considerable dose escalation of the other drugs.

Table 3 lists clinical trials that have combined thalidomide with high-dose dexamethasone and cyclophosphamide with or without additional drugs such as idarubicin or etoposide in patients with relapsed or refractory disease. The response rate varies from 55–81% (combined 64%, 95% CI 59–69%), which is as good as or better than rates in many trials of first-line treatment with VAD [10–15].

The question of combination therapy is complicated in this indication, and the optimal agents, their dose and scheduling is still to be elucidated in clinical trials and systematic reviews. It should be noted that other groups have used thalidomide in combination with different drugs, such as liposomal doxorubicin, vincristine, etc. Of greatest interest are the impressive results that have been obtained with the combination of thalidomide, prednisone and melphalan in previously untreated elderly patients; these give hope that better response rates will translate into prolonged remission duration and survival.

Randomised phase III trials are currently under way and some will soon finish recruitment. Already evident are very good response rates in thalidomide-treated patients. If the balance between efficacy and tolerance is positive for thalidomide in first-line treatment, many people's view on the drug will change for the better. A better survival rate in first-line treatment would give thalidomide a fixed place in the therapy of these patients – at least until other drugs have shown the same efficacy.

We need to know more about the toxicity of thalidomide. Although the list of possible adverse reactions is long – as with all drugs that have been evaluated for a prolonged period – some are clinically important, such as neuropathy, which is dose-limiting and in some patients irreversible. Maintenance therapy is especially complicated by the occurrence of neuropathy. We need to know more about strategies to avoid these problems, such as different dosing schedules, which may retain efficacy and reduce neuropathy. There are several other open clinical questions. First, there is some discussion about soft tissue plasmacytoma. Several small studies have shown contradictory results, and further research must be completed. Efficacy could be different due to pharmacokinetic and distribution factors. An increase of thromboembolic events of up to 30% has been seen in patients treated with thalidomide in combination with doxorubicin [16]. Thromboembolic events do not occur in higher rates with thalidomide monotherapy alone, however, and interesting further research will have to find out why the risk in-

Table 3. Combination of thalidomide (T) with cyclophosphamide (Cy) and dexamethasone (D)

Study	Combination regimen	No. of patients	Response rate (CR+PR, %)
Moehler et al., 2001; update 03 [10]	Cy 1,600 mg/m² VP16 160 mg/m² T 400 mg/day Dex 160 mg	119	55 (46–65)
Kropff et al., 2003 [11]	Cy 1,800 mg/m² T ≤400mg/day Dex 240 mg/m²	60	70 (57–81)
Dimopoulos et al., 2003 [12]	Cy 1,500 mg/m² T 400 mg/day Dex 160 mg/m²	43	67 (51–81)
Glasmacher et al., data on file	Cy 800 mg/m² IDA 40 mg/m² T ≤400 mg/day Dex 320 mg	39	59 (46–71)
Garcia-Sanz et al., 2004 [13]	Cy 50 mg/day T ≤800 mg/day Dex 160 mg	66	55 (42–67)
Gonzales-Porras et al., 2003 [14]	Cy 50 mg/day T ≤800 mg/day Dex 160 mg	59	79 (65–88)

VP16 = Etoposide; IDA = idarubicin.

creases in combination therapy and studies to identify which patients are at risk and which prophylaxis, if any, should be undertaken.

All further development of thalidomide will be a balance between the tragedy of the past and the promise of the future. From the medical point of view, I would like to quote a recent review in which thalidomide is noted as the 'first active novel, single agent for myeloma in decades' [17]. Despite all justified excitement, it should not be forgotten that the thalidomide victims see this development with ambiguous feelings: 'We will never accept a world with thalidomide in it', is a quote taken from the website of the Thalidomide Victims Association of Canada (www.thalidomide.ca). However, many victims were involved in bringing thalidomide back to clinical use in a controlled way and reluctantly accepted the necessity of this drug for other people.

In the tension of this difficult environment, we are challenged to responsibly close this circle of harm and benefit and bring a new light for the 'dark remedy'.

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